112. (Amended) The protein of Claim 111, wherein the amino acid sequence spacer [comprises] consists of amino acid residues 741 to 794 of wild-type FVIII, wherein the amino acid residue at position 794 is selected from the group consisting of threonine and leucine.

D5 Cont

113. (Amended) The protein of Claim 112, wherein the amino acid residue at position 794 is threonine.

146. (New) The protein of Claim 17, wherein the amino acid sequence spacer comprises amino acid residues 741 to 794 of wild-type FVIII, wherein the amino acid residue at position 794 is selected from the group consisting of threonine and leucine.

D6

147. (New) The protein of Claim 107, wherein the amino acid sequence spacer comprises amino acid sequence spacer 741 to 794 of wild-type FVIII, wherein the amino acid residue at position 794 is selected from the group consisting of threonine and leucine.

REMARKS

In an effort to expedite prosecution of this application and in no way conceding the validity of the Examiner's position, Applicants have amended claims 17, 21-23, 107 and 111-113, without prejudice, to further define the present invention. In particular, Applicants have amended claims 17 and 107 to further define the amino acid sequence spacer. Applicants have amended claims 21-23 and 111-113 to add the term "amino acid" before the term "residues", and in claims 22 and 112, Applicants have replaced the term "comprises" with "consists of". Applicants have also added new claims 146 and 147. Support for the amendments and new claims may be found throughout the application as filed and in particular, without limitation, at page 9, lines 6-15. Claims 17, 20-23, 27, 107, 110-113, 120, 146 and 147 are new before the Examiner.

The claims of the present invention are drawn to inactivation resistant procoagulant-active FVIII proteins which, upon activation, become heterodimers. The novel proteins of the present invention comprise modified human FVIII polypeptide lacking the B domain and von Willebrand factor binding site and having a mutation at Arg740 and an addition of an amino acid sequence spacer between the A2- and A3-domains so that upon activation, a heterodimer is achieved. The heterodimer (novel FVIIIa) has an approximate five-fold increase in specific activity compared to purified wild-type FVIII which, upon activation, becomes a heterotrimer that is unstable and subject to rapid inactivation through disassociation of the A2 subunit. Novel, inactivation resistant procoagulant-active FVIII proteins are thus provided.

I. Election/Restriction

Applicants continue to traverse the restriction requirement set forth in the Office Action mailed September 30, 1998. In an effort to expedite prosecution, Applicants will continue to prosecute the Group III invention as defined by the Examiner. Pursuant to MPEP §821.04, Applicants request that upon allowance of a compound claim within the elected invention, the Examiner rejoin the method of use claims that are commensurate in scope with the allowed claims.

II. Sequence Rule Compliance

In response to the "Notice to Comply with the Sequence Listing", Applicants submitted on February 4, 1999 a Response to Notice to Comply and Statement in Support of Submission of Sequence Data with a hard-copy of the sequence listing and computer diskette.

III. Drawings

Applicants note the requirement of formal drawings and will submit same upon notice of allowance.

IV. 35 U.S.C. §112, Second Paragraph

The Examiner has rejected claims 17, 20-23, 27, 107, 110-113 and 120 under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention. In particular, the Examiner states that A) the phrase "procoagulant-active FVIII protein" in claims 17 and 107 is indefinite; B) the term "the B domain" in claims 17 and 107 lacks antecedent basis; C) the term "von Willebrand factor binding site" in claims 17 and 107 lacks antecedent basis; D) the term "the A2- and A3 – domains" in claims 17 and 107 lacks antecedent basis; E) the phrase "a mutation at Arg740" in claims 17 and 107 is unclear to the metes and bounds of "mutation"; F) the phrase "comprises residues 741 to 794 of wild-type factor FVIII" and "position 794...threonime" in claims 17 and 107 lacks antecedent basis; G) the term "comprises residues 741-794" in claims 22 and 112 is confusing as being dependent on claims 21 and 111 requiring a 54 amino acid residue spacer; and H) the term "residue(s)" in claims 21-23 and claims 111-113 should specify "amino acid residues". The Examiner has also rejected claims 22, 23, 112 and 113 under 37 C.F.R. §1.75 as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicants respectfully traverse and request reconsideration.

With respect to rejection A), Applicants submit that the phrase "procoagulant-active FVIII protein" is clear and definite to one skilled in the art and, contrary to the Examiner's assertion, after reading the specification, one skilled in the art would know the initial polypeptide structure for the claimed proteins. The specification describes

known DNA sequences encoding human FVIII and methods for modifying the known sequences to provide the claimed modified proteins. Applicants refer the Examiner to the specification at page 2, lines 5-19 and lines 25-30, page 10, lines 16-35 (and the references incorporated therein), page 11, lines 1-3 and 18-32, Example 3, and Figure 1A, for a detailed description of the procoagulant-active FVIII proteins of the present invention and methods of making same. Moreover, Applicant refers the Examiner to U.S. Patent No. 5,004,803 (incorporated by reference at page 10, line 29 of the present application) and U.S. Patent No. 5,451,521, which contain claim language similar to the now pending claims. Applicants submit that the structure of human FVIII is known in the art and, in addition, the specification describes in detail the structure of the modified human FVIII polypeptides as claimed. Applicants thus request withdrawal of the rejection.

With respect to rejections B) – D), the structure of human FVIII protein is well known to those skilled in the art and, as set forth above, is also set forth in the specification (see, *e.g.*, page 2, lines 5-35, page 10, lines 16-35 and the references incorporated therein, and Figure 1A). It is therefore unnecessary to reiterate the structure of human FVIII in order to define the modified, claimed human FVIII polypeptides. (Applicants again refer the Examiner to U.S. Patent No. 5,004,803 for accepted claim language). Applicants therefore request withdrawal of these rejections.

With respect to rejection E), Applicants submit that the phrase "a mutation at Arg740" is clear and definite and refer the Examiner to page 10, lines 25-26 of the specification, which describes a "mutation" as "any alteration including but not limited to substitutions, insertions and deletions." Applicants further direct the Examiner to the Examples and in particular, Example 3 at page 22, lines 26-27, which describe an Arg740

mutation. Applicants thus submit that the claims as filed are clear and definite and request withdrawal of the rejection.

With respect to rejection F), independent claims 17 and 107 state that the modification in the human FVIII polypeptide comprises/consists of "a deletion of the B domain...and an addition of an amino acid sequence spacer." Claims 22-23 and 112-113, which are dependent upon claims 17 and 107, respectively, further define the additional amino acid sequence spacer. Thus, the claimed human FVIII although B-domainless, may contain an additional amino acid sequence that happens to have a sequence that is identical to a portion of the B domain. Applicants thus submit that the claims are clear and definite with respect to these modifications and request withdrawal of the rejection.

With respect to rejections G), H) and the rejection under 37 C.F.R. § 1.75(c), Applicants have amended claims 21-23 and 111-113 to add the phrase "amino acid" before the word "residues" and, in claims 22 and 112, Applicants have substituted the term "comprises" with "consists of". Applicants submit that these amendments render the rejections moot and therefore request withdrawal of the rejections.

V. 35 U.S.C. §102(b)

The Examiner has rejected claims 17, 27, 107 and 120 under 35 U.S.C. §102(b) as being anticipated by WPIDS English Abstract 88-362113 of European Application No. 295597 ("EP abstract"). The Examiner states that the EP abstract discloses a FVIII derivative compound which lacks the B domain and the VWF binding site and which possesses a mutated Arg740 which acts as an amino acid sequence spacer. Applicants respectfully traverse and request reconsideration.

The EP abstract describes a FVIII derivative that lacks the 741-1689 amino acid region of the native protein and has "a new site at Arg-740". The claimed procoagulant-active FVIII proteins comprise a modified human FVIII polypeptide also having a mutation at Arg740 "and an addition of an amino acid sequence spacer". The EP abstract does not disclose or suggest an amino acid sequence spacer. Moreover, the Examiner's assertion that a mutated Arg740 "acts as an amino acid sequence spacer", is clearly without merit when the present claims recite both a mutation at Arg740 and an amino acid sequence spacer. Applicants submit that the Examiner is improperly reconstructing the EP abstract in light of the present invention, to include elements that are taught by the present invention but are clearly not disclosed or suggested by the EP abstract.

Moreover, in an effort to expedite prosecution of this application and in no way conceding the validity of the Examiner's arguments, Applicants have amended the claims to further define the amino acid sequence spacer as "of a sufficient length so that upon activation, the procoagulant-active FVIII protein becomes a heterodimer." Clearly the EP abstract does not teach or suggest such a protein. Applicants thus request withdrawal of the rejection.

VI. 35 U.S.C. § 103

The Examiner has rejected claims 17, 20-22, 27, 107, 110-112 and 120 under 35 U.S.C. §103(a) as being unpatentable over the EP abstract and U.S. Patent No. 5,451,521 ("'521 patent"). The Examiner states that the EP abstract teaches a FVIII derivative compound that lacks the B domain and the VWF binding site and which possesses a mutated Arg740. The Examiner asserts that the EP abstract differs from the claimed invention by failing to recite the Arg740 mutation (Arg to Ala) and the use of a spacer. (Query whether the above §102(b) rejection is therefore appropriate.) The Examiner states that the '521 patent discloses procoagulant factor FVIII derivatives of the formula

A-x-B, wherein A is amino acid residues 1-372 of human FVIII, B is amino acid residues 1690-2332 of human FVIII and x is a linking moiety. The Examiner then states that the '521 patent provides motivation to attach the A1-A2 heavy chain fragment to the C1-C2 light chain fragment utilizing amino acid linkers derived from the B chain. The Examiner also states that the '521 patent teaches the replacement of the Arg residue at position 740 with non-conservative amino acid substitutions such as Ile, in order to obtain proteolytic resistance and thus substitution of Arg740 with other non-conservative amino acids which possess similar side chain properties to Ile, would have been obvious. The Examiner then asserts that modifying the EP abstract to incorporate a linking peptide which comprises B-chain residues and the further substitution of Arg, would have been obvious in view of the '521 patent. Applicants respectfully traverse and request reconsideration.

As set forth above and admitted by the Examiner, the EP abstract does not disclose or suggest an amino acid sequence spacer and thus does not disclose or suggest the claimed protein. With respect to the '561 patent, it discloses a protein characterized by the amino acid sequence A-x-B, wherein A represents A1a-1 through Arg-372 and B represents Ser-1690 through Tyr-2332 of human FVIII, and x represents 0-1316 amino acids substantially duplicative of Arg-372 through Ser-1690 of a full-length sequence of FVIII. Neither reference, either alone or in combination, teach or suggest a procoagulant-active FVIII protein comprising a human FVIII polypeptide that is modified, wherein the modification comprises a mutation at Arg 740 and an addition of an amino acid sequence spacer. Likewise, neither reference, either alone or in combination, teach or suggest a procoagulant-active FVIII protein that upon activation by thrombin achieves a heterodimer, let alone the now claimed procoagulant-active FVIII protein having an amino acid sequence spacer between the A2- and A3- domains, wherein the amino acid sequence spacer is of a sufficient length so that upon activation,

the procoagulant-active FVIII protein becomes a heterodimer. The claims as amended are thus not taught or suggested by the prior art and thus Applicants request withdrawal of the rejection.

Again, no concession is made to the validity of the Examiner's rejections and Applicants' remarks made herein are for purposes of further clarifying for the Examiner Applicants position so that upon further examination it will be clear to the Examiner that the claimed invention, from the outset, is patentable. There is no intention to surrender any range of equivalents by the remarks made herein. The remarks are made in the interest of orderly prosecution and to secure expedited allowance of the application.

SUMMARY

The claims are believed to be in condition for allowance, and such action is respectfully requested. If a telephone conversation with Applicants' representative would expedite the prosecution of the above-identified application, the Examiner is urged to call Applicants' representative at (617) 227-7400.

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